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Synthesis of Amines by Reductive Amination of Aldehydes and Ketones using Co_3O_4/NGr@C Catalyst

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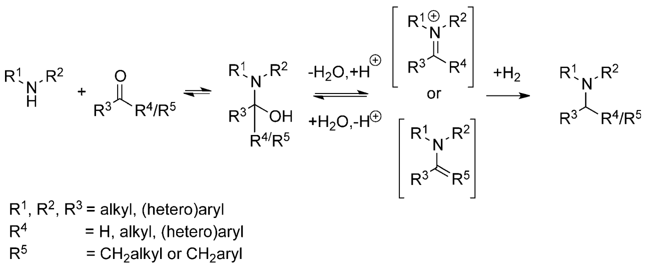
Heterogenized non-noble metal-based catalysts allow for cost-efficient and environmentally benign hydrogenations. Here, we have developed a straightforward reductive amination methodology using molecular hydrogen in the presence of a Co_3O_4/NGr@C catalyst system. Various carbonyl compounds were transformed with secondary amines to the corresponding tertiary amines with good to excellent yields and selectivity. The Co_3O_4/NGr@C catalyst is recycled up to five times without significant loss of activity.

Tertiary amines are common motifs found in numerous organic building blocks, industrial fine chemicals, agrochemicals and pharmaceuticals. For their synthesis the direct reductive amination (DRA) of carbonyl compounds is an efficient and straightforward method.[1] It allows the formation of a variety of substituted amines starting from easily available carbonyl compounds. Typically, the process is performed as a one pot reaction with imines, enamines, or iminium cations as intermediates followed by subsequent reduction (Scheme 1).



Scheme 1. Direct reductive amination of aldehydes and ketones.

Although organometallic hydrides, for example, borohydrides, are established reducing agents for this transformation on a small scale,[2] in industry catalytic hydrogenation with molecular hydrogen prevails. Since the first report in 1921, using a heterogeneous nickel-based catalyst by Mignonac,[3] numerous solid catalysts have been developed for this reaction. Today, clearly Pd/C is the most commonly used catalytic system for reductive aminations.[4] Apart from that, supported Pt-, Ru-, Rh- and Cu-based catalysts are used occasionally.[5,6] Notably, most of the previous work is concerned with the reductive amination of carbonyl compounds using primary amines, while the present work focusses on the synthesis of tertiary amines.

Recently, we synthesized novel heterogeneous cobalt oxide catalysts by pyrolysis of $Co(OAc)_2$ and 1,10-phenanthroline on Vulcan XC72R as carbon support. Pyrolysis at 800 °C under inert conditions led to active hydrogenation and oxidation catalyst systems.[7] Regarding the catalyst structure, we observed fractions of well pronounced cobalt-based nanoparticles with varying sizes of 2–20 nm, as well as particles and agglomerates in the range of 20–200 nm. Notably, these particles are encapsulated by individually nitrogen-enriched graphene-type layers,[8] which are formed in the pyrolysis process by carbonization of the nitrogen ligand. On the basis of this work, we became interested to explore the resulting Co_3O_4/NGr@C material in reductive amination reactions of carbonyl compounds and secondary amines to give tertiary amines.

At the start of this project, we examined the reductive amination of benzaldehyde with dibenzylamine as a model reaction. Based on the initial optimization, the use of 3 mol % catalyst, a molar ratio of 0.5:0.75 of amine/aldehyde and 50 bar hydrogen pressure led to best results (Table 1). The conversion reported above is related to the conversion of the amine. The residual carbonyl component is mainly reduced to the corresponding alcohol, which can be easily distilled off in the purification procedure. Notably, the choice of solvent has a pronounced effect on the activity of the catalyst. Even though we have chosen toluene as our solvent, since it gave the best results under the optimized conditions, we investigated this effect in more detail. Contrary to previous work on reductions of nitro compounds,[7a,9] the use of aromatic solvents gave optimal results and the desired product is formed in 95 % yield.

To demonstrate the general applicability of the catalyst in reductive aminations, various aldehydes and ketones were tested in reactions with secondary amines (Tables 2 and Figure 1). Gratifyingly, substrates with halogen, hydroxy, ether, and thioether groups are smoothly hydrogenated (Table 2, entries 3–6 and 13). Moreover, aliphatic aldehydes give moderate to good yields (Table 2, entries 9, 12, 15). However, lower yield was obtained for 4-phenylbutanal compared to the simple aliphatic aldehyde. This may be attributable to steric hindrance. Interestingly, both 4′-(methylthio)acetophenone and 2-naphthaldehyde gave excellent yields of the corresponding tertiary amines (Table 2, entries 8 and 13). Using less nucleophilic diphenylamine as substrate the respective tertiary amine was ob-

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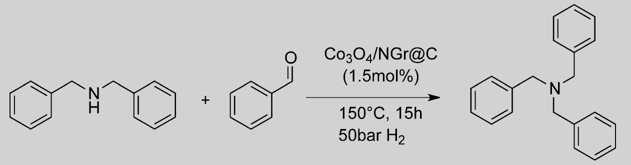
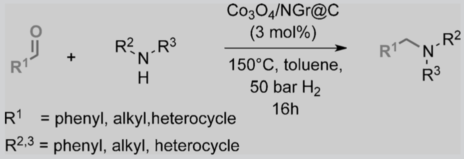
Table 1. Reductive amination of benzaldehyde with dibenzylamine: Variation of reaction parameters.[a]



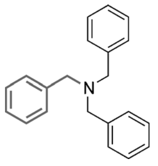
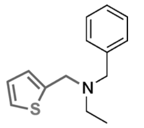
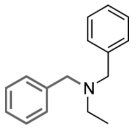
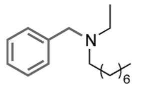
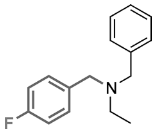
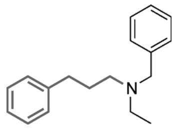
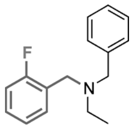
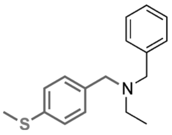
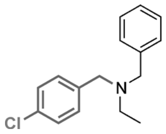
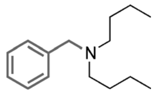
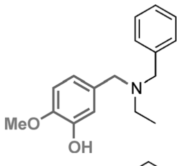
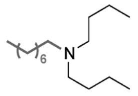
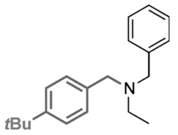
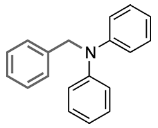
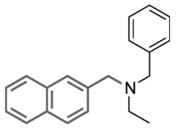
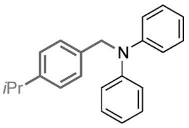
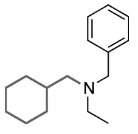
Entry	Solvent	Conversion[b]	Yield[c]
1	THF/H_2O[b]	50	50
2	THF	70	70
3	toluene	90	90
4	toluene	85[d]	85[d]
5	toluene	40[e]	40[e]
6	toluene	85[f]	85[f]
7	toluene	95[g]	95[g]
8	acetonitrile	85	80
9	1,4-dioxane	80	80
10	*o*-xylene	80	80
11	dibutylether	80	80

[a] Reaction conditions: 0.5 mmol dibenzylamine, 0.75 mmol benzaldehyde, Co_3O_4/NGr@C (1.5 mol%), 150 °C, 15 h, 50 bar H_2. [b] THF/H_2O 10:1. [c] Yield determined by GC. Hexadecane as internal standard. [d] Co_3O_4/NGr@C (1.5 mol%); $CoBr_2$ was used as the Co-precursor. [e] Co_3O_4/NGr@C (1.5 mol%) pyrolized under NH_3-atmosphere. [f] Co_3O_4/NGr@C (1.5 mol%) was prepared with Vulcan XC72R activated by H_2O_2. [g] 3 mol% Co_3O_4/NGr@C.

Table 2. Reductive amination of aldehydes with diaryl- or dialkylamines.[a]



R^1 = phenyl, alkyl,heterocycle
$R^{2,3}$ = phenyl, alkyl, heterocycle

Entry	Product	Yield[b] [%]	Entry	Product	Yield[b] [%]
1		95	10		65
2		76	11		68
3		57	12		46
4		62	13		80
5		57	14		72
6		65	15		70
7		62	16		< 10[d]
8		69[c]	17		< 10[d]
9		58[c]			

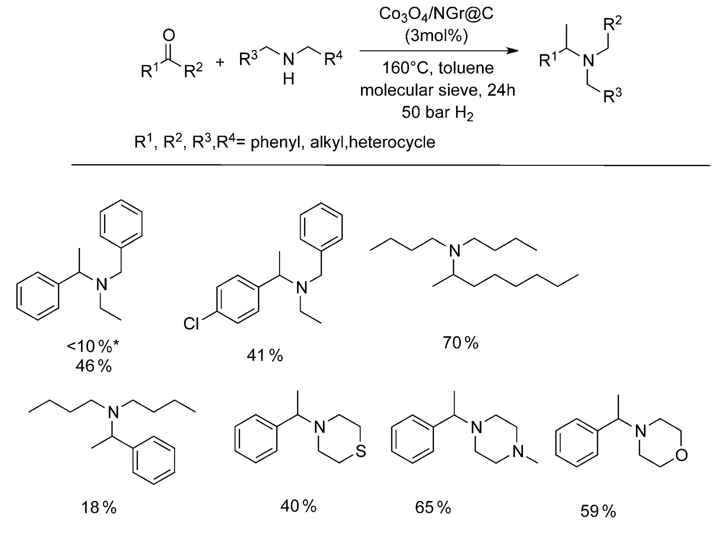
[a] Reaction conditions: 1.5 mmol of amine, 2.25 mmol of aldehyde, Co_3O_4/NGr@C (3 mol%), 150 °C, 16 h, 50 bar H_2 [b] Yields were isolated by distillation under reduced pressure. [c] Yield in total, deducting all impurities [d] Detected by GC-MS.

tained in yields below 10% (Table 1, entries 16 and 17). In general, the reduction of the aldehyde to the corresponding alcohol was also observed as a side reaction.

Owing to steric hindrance the application of ketones in the reductive amination is more challenging. Here, the formation of the iminium intermediate is disfavored in the equilibrium; hence elevated temperature and prolonged time are required for the reaction with ketones (Figure 1). To remove the formed water and to get complete conversion, molecular sieves (4 Å) were added. Indeed, the yield increased from < 10% to 46% for the reaction of acetophenone and *N*-ethylbenzylamine. With respect to reactivity, for ketones a similar tendency as in case of aldehydes is observed. Growing steric hindrance and electrophilicity caused a decrease of the yield. Comparing the reaction of benzaldehyde and acetophenone with aliphatic diamines significantly lower yield was observed for the ketone. To our delight, heterocyclic amines tend to give good yields in this process.

An important aspect for the practical use of any heterogeneous catalyst is the possibility to recycle the material easily. Thus, we investigated the recycling of our system for the original benchmark reaction. As shown in Figure 2, the catalyst was recycled up to five times with a slight loss of activity (≈10%). Nevertheless, the yield of the product *N*,*N*-dibenzyl-*N*-ethylamine remained at ≈80% after five cycles. Notably, the larger scale reactions resulted in higher yields (compared to entry 2, Table 2). This can be explained by some evaporation of the substrates/products out of the reaction vessel, which on small scale (0.5 mmol) had a pronounced negative impact.

In conclusion, we have demonstrated that nanostructured cobalt oxides represent a general catalytic system for the selective reductive amination of aldehydes and ketones. The synthesis of different tertiary amines proceeds in moderate to good yields without any additives.



* without molecular sieves

Figure 1. Reductive amination of ketones with diaryl- or dialkylamine.

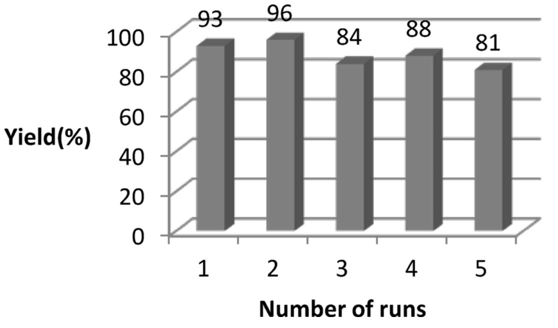


Figure 2. Recycling experiments of model reaction: reductive amination of benzaldehyde with *N*-ethylbenzylamine. Reaction conditions: 5 mmol *n*-ethylbenzylamine, 7.5 mmol benzaldehyde, 150 °C, 15 h, 50 bar H_2.

Experimental Section

General procedure for the reductive amination of aldehydes and ketones: An 8 mL vial containing a stirrer bar was charged with the respective aldehyde or ketone (1.75 mmol) and dissolved in dry toluene (3 mL). Then, the amine and carbon-supported cobalt catalyst (3 mol % Co) was added. In case of ketones additional molecular sieves (4 Å) are needed. The vials (up to 7) were placed into a 300 mL autoclave, which was flushed with hydrogen twice and pressurized to 50 bar hydrogen. It was placed into an aluminum block, heated up to 150 °C or 160 °C, and stirred for the indicated time (16 h/24 h). After the reaction, the autoclave was cooled to room temperature and depressurized. The catalyst was filtered off on silica gel and the filtrate was concentrated under reduced pressure. The residue was distilled under reduced pressure to obtain the final product.

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Keywords: reductive amination · aldehyde · ketone · heterogeneous catalysis · cobalt catalyst

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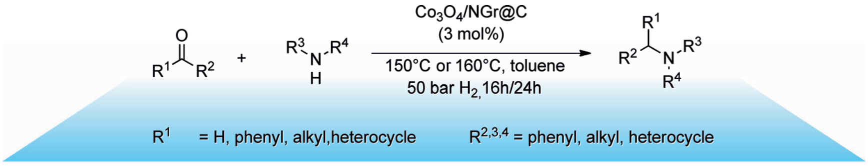

A cobalt from the blue: Heterogenized cobalt oxide-based catalysts (Co_3O_4/NGr@C) allow for reductive aminations of aldehydes and ketones. Diverse carbonyl compounds were transformed with secondary amines to the corresponding tertiary amines with moderate to high yields in good selectivity. The Co_3O_4/NGr@C catalyst was recycled up to five times without significant loss of activity.